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L3: Entry 4 of 109 File: USPT Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6033708 A
TITLE: Method for producing sterile filterable liposome dispersion

BSPR:
One important characteristic of a regulatory approved blood substitute or parenteral product is that it be sterile. Terminal sterile filtration is preferred to aseptic processing for the generation of a sterile parenteral product, and has been found to be the most effective in terms of processing and liposome stability. The best method for terminal sterile filtration is the sequential filtration of a dispersion of liposomes through a 0.45 and 0.22 um filtration system, and liposomes larger than 0.2 um, or aggregation of smaller liposomes will obstruct and clog this filter system as well as the ultrafiltration system employed to remove unentrapped components. The Farmer patents disclose the small scale filtration of a liposome encapsulated hemoglobin formulation dispersed in a hyperosmotic buffered saline solution through a 0.22 um filter. Similarly, Djordjevich discloses a laboratory process for filtering liposome encapsulated hemoglobin dispersed in a saline solution through a 0.22 micron filter for purposes of sterilization.

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L3: Entry 25 of 109 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885260 A
TITLE: Freeze-dried liposome delivery system for application of skin treatment agents

DEPR:
Administration to humans requires that the liposomes be pyrogen-free and sterile. To eliminate pyrogens, pyrogen-free raw materials, including all chemicals as well as the agents and water are used to form the liposomes. Sterilization can be performed by filtration of the liposomes through a 0.2 micron filter. A general discussion of liposomes and liposome technology can be found in a three volume work entitled Liposome Technology edited by G. Gregoriadis, 1993, published by CRC Press, Boca Raton, Fla. The pertinent portions of these references are incorporated herein by reference.

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L3: Entry 32 of 109 File: USPT Nov 17, 1998

DOCUMENT-IDENTIFIER: US 5837282 A
TITLE: Ionophore-mediated liposome loading

DEPR:
Typically, the major lipid component in the liposomes is phosphatidylcholine. Phosphatidylcholines having a variety of acyl chain groups of varying chain length and degree of saturation are available or may be isolated or synthesized by well-known techniques. In general, less saturated phosphatidylcholines are more easily sized, particularly when the liposomes must be sized below about 0.3 microns, for purposes of filter sterilization. Phosphatidylcholines containing saturated fatty acids with carbon chain lengths in the range of C.sub.14 to C.sub.22 are preferred. Phosphatidylcholines with mono or diunsaturated fatty acids and mixtures of saturated and unsaturated fatty acids may also be used. Other suitable lipids include phosphonolipids in which the fatty acids are linked to glycerol via ether linkages rather than ester linkages. Liposomes useful in the present invention may also be composed of sphingomyelin or phospholipids with head groups other than choline, such as ethanolamine, serine, glycerol and inositol. Preferred liposomes will include a sterol, preferably cholesterol, at molar ratios of from 0.1 to 1.0 (cholesterol:phospholipid). Most preferred liposome compositions are distearoylphosphatidylcholine/cholesterol, dipalmitoylphosphatidylcholine/cholesterol, and sphingomyelin/cholesterol. Methods used in sizing and filter-sterilizing liposomes are discussed below.

DEPR:
The liposome compositions prepared by the methods described above can be administered either alone or in mixture with a physiologically-acceptable carrier (such as physiological saline or phosphate buffer) selected in accordance with the route of administration and standard pharmaceutical practice. Generally, normal saline will be employed as the pharmaceutically acceptable carrier. Other suitable carriers include, e.g., water, buffered water, 0.4% saline, 0.3% glycine, and the like, including glycoproteins for enhanced stability, such as albumin, lipoprotein, globulin, etc. In compositions comprising saline or other salt containing carriers, the carrier is preferably added following liposome formation. Thus, after the liposome is formed and loaded with a suitable drug, the liposome can be diluted into pharmaceutically acceptable carriers such as normal saline. These compositions may be sterilized by conventional, well known sterilization techniques. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may also contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, etc. Additionally, the composition may include lipid-protective agents which protect lipids against free-radical and lipid-peroxidative damages on storage. Lipophilic free-radical quenchers, such as .alpha.-tocopherol and water-soluble iron-specific chelators, such as ferrioxamine, are suitable.

DEPR:
Preferably, the pharmaceutical compositions are administered parenterally, i.e., intraarticularly, intravenously, intraperitoneally, subcutaneously, or intramuscularly. More preferably, the pharmaceutical compositions are administered intravenously or intraperitoneally by a bolus injection. For example, see Raham et al., U.S. Pat. No. 3,993,754; Sears, U.S. Pat. No. 4,145,410; Papahadjopoulos et al., U.S. Pat. No. 4,235,871; Schneider, U.S. Pat. No. 4,224,179; Lenk et al., U.S. Pat. No. 4,522,803; and Fountain et al., U.S.

Pat. No. 4,588,578. Particular formulations which are suitable for this use are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Typically, the formulations will comprise a solution of the liposomes suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.9% isotonic saline, and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

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L3: Entry 47 of 109 File: USPT Jul 7, 1998

DOCUMENT-IDENTIFIER: US 5776486 A
TITLE: Methods and apparatus for making liposomes containing hydrophobic drugs

BSPR:
Present liposome products are difficult to sterilize. Sterility is currently accomplished by independently sterilizing the component parts--lipid, buffer, drug and water--by autoclave or filtration and then mixing in a sterile environment. This sterilization process is difficult, time consuming and expensive since the product must be demonstratively sterile after several processing steps.

BSPR:
Heat sterilization of the finished product is not possible since heating liposomes does irreparable damage to liposomes. Filtration through 0.22 micron filters may also alter the features of multilayered liposomes. Gamma ray treatment, not commonly used in the pharmaceutical industry, may disrupt liposome membranes. Picosecond laser sterilization is still experimental and has not yet been applied to the sterilization of any commercial pharmaceutical.

L3: Entry 65 of 109 File: USPT Dec 31, 1996

DOCUMENT-IDENTIFIER: US 5589189 A
TITLE: Liposome dispersion

BSPR:
One important characteristic of a regulatory approved parenteral product is that it be sterile. Terminal sterile filtration is preferred to aseptic processing for the generation of a sterile parenteral product, and has been found to be the most effective in terms of processing and liposome stability. The best method for terminal sterile filtration is the sequential filtration of a dispersion of liposomes through a 0.45 and 0.22 micron filtration system, and liposomes larger than 0.2 .mu.m or aggregations of smaller liposomes will obstruct and clog this filter system, as well as the ultrafiltration system employed to remove unentrapped components. The Farmer patents disclose the small scale filtration of a liposome encapsulated hemoglobin formulation dispersed in a hyperosmotic buffered saline solution through a 0.22 micron filter. Similarly, Djordjevich discloses a laboratory process for filtering liposome encapsulated hemoglobin dispersed in a saline solution through a 0.22 micron filter for purposes of sterilization.

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L3: Entry 72 of 109 File: USPT Sep 10, 1996

DOCUMENT-IDENTIFIER: US 5554382 A
TITLE: Methods and apparatus for making liposomes

BSPR:
Present liposome products are difficult to sterilize. Sterility is currently accomplished by independently sterilizing the component parts--lipid, buffer, drug and water--by autoclave or filtration and then mixing in a sterile environment. This sterilization process is difficult, time consuming and expensive since the product must be demonstratively sterile after several processing steps.

BSPR:
Heat sterilization of the finished product is not possible since heating liposomes does irreparable damage to liposomes. Filtration through 0.22 micron filters may also alter the features of multilayered liposomes. Gamma ray treatment, not commonly used in the pharmaceutical industry, may disrupt liposome membranes. Picosecond laser sterilization is still experimental and has not yet been applied to the sterilization of any commercial pharmaceutical.

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L3: Entry 109 of 109 File: DWPI Aug 27, 1991

DERWENT-ACC-NO: 1991-273765
DERWENT-WEEK: 199137


TITLE: Treatment of neoplasms esp. liver neoplasms in humans - comprises admin. of liposome encapsulated drug giving reduced side effects over free drug

ABTX:
Treating neoplasms in human patient comprises; preparing for parenteral admin. an aq. suspension of liposomes (i) whose lipid bilayer region contains at least 25 mole % of an anthraquinone drug (I) or its pharmacologically acceptable salt, and (ii) which are sized to allow sterilisation by filtration through a 3.45 micron pore size membrane, the suspension contg. 20% (I) in the free form; and parenterally administered in a pharmacologically acceptable amt. of the suspension.

L3: Entry 104 of 109 File: USPT Apr 12, 1988

DOCUMENT-IDENTIFIER: US 4737323 A
TITLE: Liposome extrusion method

DEPR:
In a typical processing operation, a suspension of heterogeneous size liposomes are placed in vessel 28, and the valves are set initially to pump the suspension through the filter apparatus in a forward direction. As will be seen from the procedure described in Examples II and III, and according to an important finding of the present invention, a single passage through the 1.0 micron pore size filter apparatus reduces the average liposome size to about 0.3-0.35 microns, with a standard size deviation of about 40%. These size characteristics are suitable for purposes of subsequent filter sterilization and to desirable therapeutic properties. Alternatively, the suspension may be recycled through the filter apparatus, and preferably by alternating the flow in forward and backward directions, to reduce the average size of the liposomes selectively. For example, as described in Example II, cycling the above MLV suspension through the 1.0 pore-size filter several times gradually reduced the liposome average size from 0.3 microns (after one filtration) to about 0.2 microns (after several passes). Cycling the material alternately in a back direction acts to prevent particle build-up and clogging at the filter's inner surface.

DEPR:
The size-processed liposome suspension may be readily sterilized by passage through a sterilizing membrane having a particle discrimination size of about 0.2 microns, such as a conventional 0.22 micron depth membrane filter. The sterilizing filter may be an asymmetric ceramic filter of the type described above, but having an inner surface pore size of about 0.2. However, since an asymmetric filter will produce some liposome sizing effect, with the attendant possibility of higher pressure requirements and/or eventual membrane clogging, a conventional membrane filter is preferred for sterilization. Also, the tortuous path pore structure of conventional sterilizing membrane filters is preferred for maximum bacteria retention.

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